Bilateral Repetitive Transcranial Magnetic Stimulation Combined With Task Oriented Training in Stroke: Randomized Controlled Trial.

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Abstract

Background

Repetitive transcranial magnetic stimulation (rTMS) changes the excitability of the motor cortex and thereby has the potential to enhance motor recovery after stroke. Task oriented training is an interventional method that has proved effective inrestoration of abnormalpatterns in both the damaged hemisphere and the contralateral hemisphere.The purpose of this study is to evaluate the efficacy of bilateralrTMS as an adjunct to task-oriented training in facilitating restoration of upper limb function after stroke.

Methods

A total of 20 first time stroke patients with upper limb motor deficits were randomly allocated into two equal groups;study group, which received five daily sessions of 5-Hz ipsilesionalrTMS (facilitatory) and 1-Hz contralesionalrTMS(inhibitory), followed bytask oriented training sessions, and control group, which received sham rTMSfollowed by task oriented training sessions.Task oriented training sessions then continued for one month at 3 sessions per week. Outcome measures included theFugl-Meyer Upper Extremity assessment, and the Wolf Motor Function Test, which were assessed at baseline (pretest) andafterone month of treatment (posttest).

Results

The results of this study showed that;there was no statistically significant difference observed in between groups on both outcome measures of upper limb function at pre and post tests

Conclusion

The present study revealed that combining rTMS with task-oriented training in improving upper limb function post stroke is not superior to task oriented training alone.

Keywords: Upper Limb Function, Repetitive Transcranial Magnetic Stimulation, Stroke, Task Oriented Training.

Introduction:

Stroke is the leading cause of adult long-term disability worldwide, particularly for the domain of the motor system. Only less than 40% of stroke survivors have achieved complete motor recovery, even after extensive rehabilitation treatment**(1).**Stroke or cerebrovascular accident is defined by world health organization (WHO) as “rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin**”(2).**

Longitudinal studies of recovery after stroke suggest that only less than 50% of patients with significant arm paresis recover useful function. Regaining lost function in the upper extremities may be more difficult to achieve than return of normal function (ambulation) in the lower extremities**(3)**.

Many interventions for improving upper limb function following stroke have been identified. Currently, no high-quality evidence can be found for any interventions that are currently used as part of routine practice**(4)**. Rehabilitation following stroke has evolved in the past 15 years from analytical training approaches to task-oriented training approaches**(5)**. Task-specific training is a term that has evolved from the movement science and motor skill learning literature and is defined as training or therapy where patients ‘practice context-specific motor tasks and receive some form of feedback. Task-specific training in rehabilitation focuses on improvement of performance in functional tasks through goal-directed practice and repetition. The focus is on training of functional tasks rather than impairment, such as with muscle strengthening**(6)**.

Neuro-imaging studies in animals and humans have provided evidence for changed activation patterns in many parts of the damaged brain following task-oriented training. In addition, movement and experience-dependent reorganization patterns have been observed in both the damaged hemisphere and the contralateral hemisphere**(7)**.

However, there are very few studies of the neural mechanisms of task- oriented training in stroke patients. Evidence supporting the potential benefit of task-oriented training for improvement of upper limb impairment are therefore inconclusive. This is mainly due to the small number of trials conducted and the small sample sizes included in them**(4).**

Based on Faradays' law of electromagnetic induction, transcranial magnetic stimulation (TMS) can be used to create magnetic field pulses, which in turn can induce electrical activity in focal brain areas. TMS of the primary motor cortex (M1) activates cortico-spinal neurons trans-synaptically, eliciting volleys of neuronal output in the form of motor evoked potentials (MEP) **(7).**

Repetitive transcranial magnetic stimulation (rTMS) involves stimulation of the cortex by a train of magnetic pulses at frequencies between 1 and 50 Hz, in contrast to single-pulse TMS in which the frequency of stimulation is less than1 Hz Repetitive TMS can either activate or inhibit cortical activity, depending on stimulation frequency . Low frequency (1 Hz) stimulation for a period of approximately 15 min induces a transient inhibition, or a decrease in activity, of the cortex. The mechanisms behind such inhibition is unclear, although there are similarities to long-term depression, a cellular experimental phenomenon where repeated low-frequency stimulation reduces activity in individual synapses. In contrast, stimulation at frequencies above 1 Hz has been shown to induce increased cortical activation. The mechanisms by which such activation occurs are also unclear, although some authors suggest that it may be due to a transient increase in the efficacy of excitatory synapses leading to long-term potentiation **(8)**.

Motor learning and task-specific practice appear to be essential for neural and functional changes to occur. rTMS enhances the effect of task-oriented training in those with chronic stroke. For example, several studies that applied rTMS alone with no other exercises did not find behavioral improvements when assessing pinch force or grip strength. On the other hand, delivery of TMS at the appropriate time during movement execution enhances the use-dependent plasticity resulting from the training, and improves pinch force. The benefit of coupling brain stimulation with physical practice may rely on Hebbian principles of synaptic plasticity, which capitalize on the temporal relationship of the interventions facilitating the formation of durable synaptic connections. Importantly though, some studies found that rTMS did not provide additive benefits to motor training. These negative results may be due to ceiling effects of the behavioral outcome measures, the complexity of the task being modulated or neural homeostatic properties of the stimulated region. Taken together, the data suggest that if the goal is to modulate behavior, the brain stimulation must be coupled with some form of training **(7).**

Although there has been extensive research on the effectiveness of repetitive transcranial magnetic stimulation (rTMS) to improve patients' motor performance after experiencing chronic stroke, explicit findings on the coupling of rTMS protocol with task-oriented training are meager **(1).**Therefore, the aim of this study is to investigate the effect of couplingbilateral rTMS with task-oriented training on upper limb function in stroke patients.

Materials and methods:

Study design:

Randomized controlled trial, with pre and post assessments.

Participants:

The current study was conducted on twenty patients (9 females and 11 males) suffering from subcortical strokes confirmed clinically and radiologically were included in this study. Patients were be selected from Al-Kasr Al-Aini hospitals outpatient clinic. They were assigned randomly into two equal studies groups

Patients included had the following criteria: diagnosed with either hemorrhagic or ischemic stroke for the first time, with an onset of more than eight weeks and not more than six months.They were aged between 40-50 years old and with Brunnstrom not less than stage Ⅲin the proximal and distal part of the arm. They had no prior experience of rTMS to confirm blindness of the intervention.Patients were excluded if they had history of seizures, any medical metal devices incompatible with rTMS (e.g. pacemaker), bi-hemispheric or multifocal stroke, premorbid neurological impairment prior to onset of stroke, co-morbidities impairing the motor function such as fracture or deformity.

The study was carried out in Al-Kasr Al-Aini hospital outpatient clinic, during the period from January 2017 to march 2018.Patients in both groups signed Informed consent form before starting the study. This study was approved by the Ethical committee of faculty of Physical Therapy, Cairo University (No: P.T.REC/012/001308).

Measurement procedures:

Assessment was done before the beginning of the program then after 4 weeks of treatment using the Fugl-meyer assessment-upper extremity (FMA-UE) scale and the wolf motor function test.

- Fugl-meyer assessment-upper extremity (FMA-UE):

The Fugl-Meyer Upper Extremity Assessment (FMA-UE) is the most widely used clinical assessment of post-stroke UE motor impairment. It has excellent intra-rater reliability, inter-rater reliability, test-retest reliability and internal consistency. It has been used as the standard in establishing the validity of other commonly used tests of UE motor function **(9).**

Scoring was based on direct observation of performance. Scale items were scored on the basis of ability to complete the item using a 3-point ordinal scale where 0=cannot perform, 1=performs partially and 2=performs fully. This study used the FMA-UE section, which allows a maximum possible score of 66 **(10).**

- The Wolf Motor Function Test (WMFT)

The WMFT quantifies upper extremity (UE) motor ability through timed and functional tasks. The WMFT was found to have good construct validity and criterion validity for stroke patients. It also had high inter-rater reliability, internal consistency, and test-retest reliability **(11).**The less affected upper extremity was tested first followed by the most affected side. The items were performed as quickly as possible, truncated at 120 seconds.

Treatment Procedures:

- Repetitive transcranial magnetic stimulation:

Five rTMS sessions were done by Magstim rapid 2, (70 mm in diameter) with figure-of-eight coil positioned tangentially over the primary motor cortex at an optimal site for the first dorsal interosseous muscle (FDI) for 5 days. The optimal site was defined as the location where stimulation at a slightly suprathreshold intensity elicited the largest motor evoked potential in the FDI **(12).**

For study group, patients received 5 sessions of alternating stimulatory 5 HZ rtms (50 stimuli of 10 seconds duration train with 5 seconds inter-train interval) for 20 trains over the ipsilateral affected motor hemisphere and sub threshold inhibitory 1HZ rTMS (50 stimuli train of 50 seconds duration train) for 20 times over the contralateral non-affected motor hemisphere with 90% of motor threshold, so 1000 pulses were applied to each hemisphere. It is difficult to apply rTMS over the affected and unaffected hemispheres simultaneously due to the mechanical limitation of the overlap of the figure-of-8 coils in the patient’s head.

For control group, patientsreceived sham stimulation by positioning the coil perpendicular to the scalp over the optimal site on both hemispheres for the same time of application for the study group.

- Task oriented training:

Task oriented training sessions for one hour were given to the patients following stimulation, for the five consecutive days of stimulation. Then sessions continued for 3 times per week for one month.

The selection of exercises for each patient were based on the principles of task-oriented training**(13).** The patient was positioned in a supported sitting position with a table in front of him. Three exercises were chosen from a list of exercises according their relevance to each patient's goal. Careful observation of the tasks was done to identify any specific component that would require specific intervention, for example muscle weakness, stiffness, etc. Each task was repeated and graded according to the patient's ability. The task difficulty level was progressed as the patient's performance improved indicated by increase in speed, accuracy and decreased compensation in the task.

Statistical analysis:

Statistical analysis was conducted using SPSS for windows, version 22 (SPSS, Inc., Chicago, IL).Mixed design MANOVA was used to compare the Fugl-meyer assessment- upper extremity and Wolf motor function test at both measuring periods for the two groups. Prior to final analysis, data were screened for normality assumption, homogeneity of variance, and presence of extreme scores. This exploration was done as a pre-requisite for parametric calculations of the analysis of difference.The alpha level was set at 0.05.

Results

- General characteristics:

Group (A) consisted of 10 patients (4 females and 6 males) with mean age, height, body mass and BMI values of 55.2±3.64 years, 1.71±0.05 m, 80.1±4.7 kg and 27.22±0.45 Kg/m2 respectively. Group (B) consisted of 10 patients (5 females and 5 males) with mean age, height, body mass and BMI values of 57.7±2.35 years, 1.71±0.05 m, 80.8±5.18 kg and 27.4±0.39

Kg/m2 respectively. As indicated by the t-test, there were no significant differences (p>0.05) in the mean values of age, body mass, height and BMI among the three tested groups (Table 1.).

Table (1).

Descriptive statistics and t-test for comparing the mean age, height, weight and BMI values for both groups.

	Group A (N=10)	Group B (N=10)	t-value	P-value	Level of significant
Age (years)	55.2±3.64	57.7±2.35	1.8247	0.0847	**N.S**
Height (m)	1.71±0.05	1.69±0.05	0.8944	0.3829	**N.S**
Body mass (kg)	80.1±4.7	80.8±5.18	0.3165	0.7553	**N.S**
Body mass index (kg/m^2)	27.22±0.45	27.4±0.39	1.0621	0.3022	**N.S**

t value: Unpaired t value **p value: Probability value** **NS: Non significant**

- Fugl-meyer assessment- upper extremity:

As presented in table (2), within group's comparison the mean ± SD values of Fugl-meyer assessment- upper extremity in the "pre" and "post "tests were 49.5 ±9.21, 54.8±8.48 respectively in the study group . Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant difference ofFugl-meyer assessment- upper extremity between pre and post assessment, with p=0.0001 and this significant increase in favor to post test in compared to pretest. Additionally, the mean ± SD values of Fugl-meyer assessment- upper extremity in the pretest and posttest were 48.2±8.72 and 57.1±6.83 respectively in the control group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant difference of Fugl-meyer assessment- upper extremity between pre and posttestwith p=0.0001and this significant increase in favor to post test in compared to pretest.

Considering the effect of the tested group (first independent variable) on Fugl-meyer assessment- upper extremity, Multiple pairwise comparison tests (Post hoc tests) revealed that the mean values of the "pre" test between the study and control groups showed no significant differences with (p=0.747). As well as, Multiple pairwise comparison tests (Post hoc tests) revealed that the mean values of the "post" test showed no significant differences between study and control groups with (p=0.501).

Table (2): Descriptive statistics and mixed design MANOVA for Fugl-meyer assessment-upper extremity at different measuring periods at two groups.

Fugl-meyer assessment- upper extremity	Pre	Post	P-value	Sig
	$\overline{X}$ ±SD	$\overline{X}$ ±SD		
Study group	49.5 ±9.21	54.8±8.48	0.0001	**S**
Control group	48.2±8.72	57.1±6.83	0.0001	**S**
P-value	0.747	0.501		
Sig	**NS**	**NS**		

$\overline{X}$ **: Mean** **SD: Standard deviation**
p value: Probability value **S: Significant** **NS: Non significant**

- Wolf motor function test:

As presented in table (3), within group's comparison the mean ± SD values of Wolf motor function test in the "pre" and "post" tests were 60.7 ±10.69 and 67.6±11.25 respectively in the study group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant difference of Wolf motor function test between pre and posttests with p=0.001 and this significant increase in favor to post test in compared to pretest. Additionally, the mean ± SD values of Wolf motor function test in the "pre" and "post" tests were 61.5±11.45 and 71.1±9.29 respectively in the control group. Multiple pairwise comparison tests (Post hoc tests) revealed that there was significant difference of Wolf motor function test between pre and posttestwith p=0.0001 and this significant increase in favor to post test in compared to pretest.

Considering the effect of the tested group (first independent variable) on Wolf motor function test, Multiple pairwise comparison tests (Post hoc tests) revealed that the mean values of the "pre" test between study and control group showed no significant differences with (p=0.785). As well as, Multiple pairwise comparison tests (Post hoc tests) revealed that there was no significant difference of the mean values of the "post" test between study and control groups with (p=0.433).

Table (3): Descriptive statistics and mixed design MANOVA for Wolf motor function test at different measuring periods at two groups.

Wolf motor function test	Pre	Post	P-value	Sig
	$\bar{X}$ ±SD	$\bar{X}$ ±SD		
Study group	60.7 ±10.69	67.6±11.25	0.0001	S
Control group	61.5±11.45	71.1±9.29	0.0001	**S**
P-value	0.875	0.433		
Sig	**NS**	**NS**		

$\bar{X}$ **: Mean** **SD: Standard deviation**
p value: Probability value **S: Significant** **NS: Non significant**

Discussion

This study was conducted to investigatethe effect of combining bilateralrTMSwith task-oriented training on upper limb function in stroke patients.The results of this study showed that; for the study group there was asignificant improvement in Fugl-meyer assessment- upper extremity and the wolf motor function test for the pre and post scores.There was also significant difference in outcome measures between pre and post assessment for the control group. However, between both groups there was no significant difference between the outcome measures scores in the pre and post assessments.

This suggests that an rTMS protocol potent enough to induce transient increases in cortical excitability of the lesioned hemisphere and cortical inhibition of the contralesional hemisphere is feasible but did not show promising results as an adjunct to task-specific training.

Our results come in agreement with **Higgins et al., (14)**., who evaluated the efficacy of rTMS as an adjunct to task-oriented therapy in facilitating restoration of arm function on 11 stroke patients. Resultsshowed nosignificant difference between the real-rTMS intervention in comparison to the sham-rTMS was found at the post intervention or at the follow-up evaluations on the Box and Block Test, WMFT and Motor Activity Log.

The results also agree with **Malcolm et al., (15)**, who tested the potential adjuvant effect of rTMS on motor learning in a group of stroke survivors undergoing constraint-induced therapy for upper-limb hemiparesis in a randomized controlled trial. Their results demonstrated significant gains in both groups on the primary outcome measures: the Wolf Motor Function Test (WMFT) and the Motor Activity Log (MAL)--Amount of Use, and on secondary outcome measures including the Box and Block Test (BBT) and the MAL--How Well. Participants receiving rTMS failed to show differential improvement on either primary outcome measure

The results also come in agreement with **Seniów et al., (16),** who evaluated the effectiveness of applying 1 Hz rTMS to the contralesional M1 in addition to physiotherapy during early rehabilitation for stroke patients with hand hemiparesis in a randomized, sham-controlled, double-blind study. No statistically significant differences were found between the experimental and the control group for the Wolf Motor Function Test or the National Institutes of Health Stroke Scale after treatment. Similar results were observed at the 3-month follow-up.

Conclusions. The findings did not suggest that rTMS augments the effect of early neurorehabilitation for upper limb hemiparesis.

On the other hand, our results contradict with **Kim and Yim (17)**, who investigated the effect of high-frequency-rTMS,combined with task-oriented mirror therapy (TOMT) on hand rehabilitation in acute stroke patients. Subjects were allocated to two groups: the experimental group received high-frequency-rTMS + TOMT and the control group received high-frequency-rTMSonly. Outcomes, including motor evoked potential (MEP), pinch grip, hand grip, and box and block test, were measured before and after training. Significant improvements in the MEP and hand function variables were observed in both groups

Our results also disagree with **Du et al., (18)**, who investigated the effect of rTMSin addition to physical therapy. The study included three groups, one received stimulatory rTMS, the second received inhibitory rTMSand the third was the control group, which received sham rTMS.Motor disability was assessed before and after the last session, and then after first, second and third month The results at the 3-month time point, both of the real rTMS groups had improved significantly more in different rating scales than the sham group

Besides our limited sample size, there may be several reasons explaining failure to detect an rTMS effect. The dose and intensity of the rTMS, although based on empirical data, may not have been optimal. Indeed studies differ greatly on this aspect and one cannot draw conclusions at this time as to the best approach to promote lasting changes in corticomotor pathways. The exact parameters with which to administer the rTMS are not well established and effects may vary greatly depending on interindividual variability such as the site and size of the lesion and the severity of the impairment, as well as intraindividual variability.

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